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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/716,174	11/17/2003	Quan Nguyen	70-000150US	3901

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EXAMINER	
YU, MELANIE J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/716,174	NGUYEN ET AL.	
	Examiner	Art Unit	
	Melanie Yu	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,21-61 and 201-221* is/are pending in the application.

4a) Of the above claim(s) *12,14-17 and 201-221* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,18,19 and 21-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 19 April 2006 has been entered. Claims 20 and 62-200 have been canceled. Claims 12, 14-17 and 201-221 have been withdrawn from consideration. Claims 1-19, 21-61 and 201-221 are currently pending in this application.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 1-11, 13 and 18-61 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 2 recite a substrate for an enzyme, but does not specifically claim an enzyme. It is unclear whether an enzyme is required as part of the composition because the composition is for detecting enzyme activity. It is unclear whether enzyme activity can be detected without the presence of an enzyme. Furthermore, if an enzyme is not required as part of the composition, it is unclear how the substrate can be converted into a second state from a first state.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 2 and 57-60 are rejected under 35 U.S.C. 102(b) as being anticipated by Barrett et al. (US 5,252,743).

Barrett et al. teach a composition comprising: a caged sensor comprising: more than one molecule collectively comprising: a substrate for an enzyme, wherein the substrate is in a first station which the enzyme can act, thereby converting the substrate to a second state, wherein the first state is not converted to the second state by cleavage of the enzyme (anti-

ligands include substrates for ligands, col. 4, lines 21-54; wherein ligands are enzymes, col. 5, lines 3-11; col. 10, lines 28-37; col. 10, lines 40-63), a first label, wherein a first signal exhibited by the first label is when the substrate is in its first state (first state is unbound with no signal and second state is bound with a signal, col. 21, lines 36-44), and one or more caging groups associated with the a molecule inhibiting an enzyme from acting on a substrate (caged biotin attached to a substrate, col. 4, lines 22-32; col. 9, lines 54-68).

Regarding claims 59 and 60, Barrett et al. teach the caged sensor comprising a first oligonucleotide complementary (ligand is an oligonucleotide, col. 5, lines 3-11) to a second oligonucleotide bound (anti-ligand is an oligonucleotide, col. 4, lines 21-54) to a matrix, which is a surface, at a predetermined location within an array (col. 10, lines 31-35) comprising other oligonucleotides (anti-ligand is bound to a matrix, col. 7, lines 43-54).

Claim Rejections - 35 USC § 103

4. Claims 1-11 and 18 are rejected under 35 USC 103(a) as obvious over Glickman et al. (US 6,806,056) in view of Burbaum et al. (US 5,981,207).

Glickman et al. teach a composition comprising: a cell (the kinase and phosphorylated substrates are in a cell, col. 7, lines 44-48) comprising a sensor for detecting activity of an enzyme comprising: one or more molecules collectively comprising: a substrate for an enzyme (binds tyrosine kinase substrate, col. 2, lines 37-40) wherein the substrate is in a first state on which the enzyme can act, thereby converting the substrate into a second state (first state is prior to phosporylation and second state is after a tyrosine residue has been phosphorylated, col. 4, line 65-col. 5, line 6), and a first label, wherein a first signal is exhibited by the first label when the substrate is in its first state is distinguishable from a second signal exhibited by the first label when the substrate is in its second state (anti-phosphotyrosine antibody is labeled and included in the compositions,

col. 5, lines 7-23). Glickman et al. fail to teach one or more first caging groups associated with the one or more molecules.

Burbaum et al. teach a first caging group associated with an enzyme substrate, inhibiting an enzyme from acting upon a substrate (col. 7, lines 36-47), in order to provide a substrate that is initially inactive and can be released into activated form at the appropriate time.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Glickman et al., a first caging group associated with an enzyme substrate inhibiting the enzyme from acting upon the substrate as taught by Burbaum et al., in order to provide an enzyme substrate that provides rapid and effective means for detecting and assessing the ability of substances to activate or suppress specific enzyme activity when short lived labels such as alkaline phosphatase are used.

Regarding claims 3-5, the claims are drawn to intended use of a composition and do not appear to require any further physical limitations. Therefore, since all physical limitations required for the composition as recited in claims 1 and 2 are taught by Glickman et al. in view of Burbaum et al., as described above, the composition of Glickman et al. in view of Burbaum et al. is capable of providing the uses recited in claims 3-5.

With respect to claim 6, Glickman et al. teach the first label being an optically detectable label wherein the second signal is a fluorescent signal (col. 11, lines 27-45; col. 9, lines 28-38).

Regarding claims 7-8, Burbaum et al. teach the caging groups being covalently attached to the enzyme substrate, wherein the caging groups are photoliabile and are removed by exposure to light of 366 nm (col. 22, lines 40-55), which is encompassed by the range of between about 60 nm and about 400 nm.

With respect to claims 9-11, Glickman et al. teach the substrate being a polypeptide (protein is with a phosphorylated tyrosine residue, col. 4, line 65-col. 5, line 6), the first label and substrate are physically connected (substrate, protein, is connected to the anti-phosphotyrosine antibody, which is labeled, therefore the fluorescent label and substrate are physically connected, col. 8, lines 9-22) and the substrate comprising one or more amino acids (protein at least contains a tyrosine residue, col. 4, line 65-col. 5, line 6). Glickman et al. also teach a cell comprising a cell lysate (col. 4, line 65-col. 5, line 6).

Regarding claim 18, Glickman et al. teach the enzyme being a protein kinase that phosphorylates tyrosine (col. 8, lines 9-22).

5. Claims 13, 19 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glickman et al. in view of Burbaum et al., as applied to claims 1 and 2, further in view of Kris et al. (US 2003/0096232).

Glickman et al. in view of Burbaum et al., as applied to claims 1 and 2, teach a composition comprising an enzyme substrate, a first label and a first caging group, but fail to teach the substrate being specific for a protease.

Kris et al. teach detection of enzyme activity wherein a substrate is specific for a kinase or a protease (par. 18 and 78), in order to provide a surface that can detect the activity of a plurality of enzymes.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the composition of Glickman et al. in view of Burbaum et al., a protease as the enzyme as taught by Kris et al., in order to identify potential blood thinners or agents which cause blood clots.

Regarding claim 19, Kris et al. also teach a polypeptide substrate (par. 18-19), wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and

first label, par. 256-258), the substrate comprising a tyrosine residue capable of being phosphorylated by the kinase (par. 256), wherein the first label is located at the tyrosine residue and exhibits a first signal when the residue is not phosphorylated and the second signal when the signal is phosphorylated (labels bind to phosphorylated substrates, and therefore bind to the phosphorylated residues, par. 258).

With respect to claim 61, Glickman et al. teach a kit comprising a substrate and a first label (col. 3, lines 16-23). Burbaum et al., as described above, teach a caging group, and Kris et al. teach including instructions for use in a kit (par. 84-87).

6. Claims 47-49 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glickman et al. in view of Burbaum et al., as applied to claims 1 and 2, further in view of Fischer et al. (Cellular Delivery of Impermeable Effector Molecules in the Form of conjugates with Peptides capable of mediating membrane translocation, 2001, Bioconjugate Chemistry, Vol. 12, No. 6, pages 825-841).

Glickman et al. in view of Burbaum et al., as applied to claims 1 and 2, teach a sensor comprising one or more molecules, but fail to teach the one or more molecules associated with a cellular delivery module.

Fischer et al. teach delivery polypeptide vectors are used to transport entire proteins into a cell (pg. 827, right column, second paragraph), in order to provide delivery of proteins that are longer than a few peptides into a cell.

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include in the substrate of the composition of Glickman et al. in view of Burbaum et al., a cellular delivery module of a polypeptide as taught by Fischer et al., in order to provide in vivo analysis of enzyme activity.

Regarding claim 49, Fischer et al. teach the cellular delivery module covalently attached to the one or more molecules (pg. 825, abstract).

With respect to claims 52-54, Fischer et al. teach that the cellular delivery module can also be used as a sub cellular delivery module by directing the proteins associated with the module to the same component (pg. 826, right column), in order to provide more accuracy. Fischer et al. teach the sub cellular delivery module being a polypeptide (pg. 827, right column, second paragraph) and covalently attached to the one or more molecules (pg. 825, abstract).

Regarding claims 50, 51, 55 and 56, Burbaum et al. teach covalently attaching a caging group to a polypeptide in order to control activation of the polypeptide (col. 7, lines 37-47).

Therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to include on the cellular delivery modules, a caging group as taught by Burbaum et al., in order to provide control for the time of introduction of the sensor into cellular components.

Response to Arguments

7. Applicant's arguments filed 19 April 2006 have been fully considered but they are not persuasive.

8. At pages 20-22, applicant argues that Barrett et al. teach caged binding members which are uncaged to permit binding of the ligand to the binding member and the caging groups which prevent binding of the ligand to the member do not affect binding of the ligand and its anti-ligand and the caging groups of Barrett et al. cannot be construed as in any way inhibiting the action of the enzyme on its substrate. However, in response to applicant's argument, this is not persuasive because according to Barrett et al., the caged binding member may be an enzyme substrate (enzyme may be a ligand, col. 5, lines 3-11, and binding member would therefore be an anti-ligand of an enzyme substrate). The caging group on the binding member of Barrett et al. prevents the ligand (enzyme) from

binding to the binding member (enzyme substrate) and therefore affect the binding of the enzyme with its substrate and therefore teach a caging group that is associated with the substrate for an enzyme and inhibits the enzyme from acting upon (binding to) the substrate. Furthermore, the instant specification teaches that the first label may be a fluorophore, which is a type of label taught by Barrett et al. Therefore the label of Barrett et al. is capable of performing the functions required of the first label, such as a first and second signal dependent on the state of a substrate.

Applicant further argues that Barrett et al. teach a label that is present on the surface if the ligand is bound to a particular anti-ligand and not present on the surface if the ligand is not bound and therefore Barrett et al. fail to teach a label whose signal is dependent on the state of the anti-ligand. Applicant argues that Barrett et al. fail to teach a first label with a first signal from the label when the substrate is in the first state that is distinguishable from a second signal from the label when the substrate is in its second state. Applicant's argument is not persuasive because the label of Barrett et al. provides no signal when the label is unbound from the enzyme substrate, when the enzyme is in its first state and provides a signal that is detectable when the enzyme is in its second state and capable of binding with the ligand. The capability of the label to bind on the substrate and subsequently be detected depends on the state of the anti-ligand and therefore the detectable signal from the label is dependent on the state of the anti-ligand.

9. At pages 22-24, applicant argues that the combination of Glickman et al. and Burbaum et al. fail to teach a label meeting the limitations of claims 1 or 2 or a cell comprising a caged sensor. Applicant argues that the label of Glickman et al. exhibits the same signal regardless of the phosphorylation state of the substrate and the label is not responsive to the state of the substrate. Applicant's argument is not persuasive because label on the second antibody does not produce a detectable signal on the support when the

antibody is in the first, unphosphorylated state. When the second antibody is phosphorylated and in the second state, the substrates are captured on a solid support and a signal is exhibited. Therefore, the label of Glickman produces a first signal when the substrate is in a first, unphosphorylated state and the label produces a second signal when the substrate is in a second, phosphorylated state. Applicant also argues that Glickman fail to teach a cell comprising the sensor because the substrate may be initially inside a cell, it is removed from the cell for binding to the solid support and contact with the labeled antibody. However, in response to applicant's arguments, the cells are assayed for kinase activity and are therefore not removed from the cell, the cell is bound to the substrate to assay phosphorylation and therefore the labeled antibodies are bound to the substrate in the cell and therefore the cell is considered to comprise the first label. Regarding claim 9, applicant's argue that the substrate and the labeled antibody of Glickman are two discrete molecules and are not joined or linked by any physical connection. In response to applicant's arguments, the labeled antibody is bound to the phosphorylated proteins in the cell lysate and therefore the label is joined to the substrate through binding. Applicant argues that claims 3-5 specify physical properties of the caging groups. However, the claims do not specify the structural limitations of the caging group required to obtain these physical properties. Applicant must show that the caging groups of the recited references are not capable of being used for the uses recited in claims 3-5. Furthermore, the instant specification states that the first label may be a fluorophore, which is a type of label taught by Glickman et al. Therefore the label of Glickman et al. is capable of performing the functions required of the first label, such as a first and second signal dependent on the state of a substrate.

1. At pages 24-26, with respect to claim 19, applicant argues that Kris et al. teach a separate substrate and antibody, which are still two distinct polypeptides, and therefore fail

to teach a single polypeptide. However, in response to applicant's arguments, claim 19 has open claim language "comprising" and therefore only one polypeptide is required to read on the claims, but the presence of multiple polypeptides is not excluded due to the open claim language. The labeled antibody binds to the phosphorylated substrate, therefore the single polypeptide substrate comprises a labeled antibody. The fact that the labeled antibody is a second polypeptide is irrelevant. Applicant further argues that the label of Kris et al. is bound to an antibody and is not attached to the substrate at all. However, in response to applicant's arguments, although the label is attached to the substrate through the antibody, the claim does not require the label to be directly attached to the substrate. The open claim language "comprising" allows for intermediate elements to be present between the substrate and the label. Since the antibody binds to the tyrosine residue of the phosphorylated kinase, the label is bound to the substrate through the tyrosine residue and reads on the instant claims. Applicant also argues that the label of Kris et al. is not responsive to the state of the substrate and that the label on the antibody exhibits the same signal regardless of the phosphorylation state of the substrate. In response to applicant's arguments, the label of Kris et al. provides no signal when the label is unbound from the substrate, when the substrate is in its first state and provides a signal that is detectable when the substrate is in its second state and capable of binding with the labeled antibody. The capability of the label to bind on the substrate and subsequently be detected depends on the state of the substrate and therefore the detectable signal from the label is dependent on whether the substrate is in its first or second state.

Regarding arguments on pages 26-28, against the rejections made under 35 USC 112, second paragraph. Applicant's arguments are not persuasive because the claim still appears to be omitting essential elements amounting to a gap between elements. See MPEP § 2172.01. The enzyme appears to be required in order for the composition to function.

The claim is unclear as to how the substrate can be in both its first and second state in the composition without the presence of an enzyme.

Allowable Subject Matter

2. Claims 21-46 are free of the prior art for the reasons stated in the previous office action dated 16 December 2005.

Conclusion

3. Claims 21-46 are free of the prior art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Melanie Yu whose telephone number is (571) 272-2933. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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